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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

FOSTER, CHRISTINE E

ART UNIT	PAPER NUMBER
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1641

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,790	YAMAZAKI ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 April 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7, 10 and 26-43 is/are pending in the application:
- 4a) Of the above claim(s) 26-33, 37-39, 41 and 43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7, 10, 34-36, and 40 is/are rejected.
- 7) ☒ Claim(s) 42 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Amendment

1. Applicant's amendment, filed 4/24/07, is acknowledged and has been entered. Claims 1, 4, 26, 29, 36, and 39 were amended. Claims 1-7, 10, and 26-43 are pending in the application, with claims 26-33, 37-39, 41, and 43 currently withdrawn.

Manner of making amendments under 37 CFR § 1.121

2. Applicant is reminded of the proper format for amendments to the claims. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn — currently amended." See MPEP 714. Specifically, claims 26-33, 37-39, 41 and 43 are accompanied by the status identifiers "currently amended" or "original" in the current claim set, yet the claims were previously withdrawn from consideration (see the Office actions mailed 10/24/06 and 5/9/06, and the requirement for restriction mailed 6/29/05).

Objections/Rejections Withdrawn

3. The rejection of claim 36 under 35 USC 112, 1st paragraph as containing new matter is withdrawn in response to Applicant's amendments to delete the term "plasma membrane vesicle" from the claim.

4. The rejections of claims 4-7 under 35 USC 112, 2nd paragraph are withdrawn in response to Applicant's amendments to recite that the label is *attached*.

5. The rejections of claims 1-2, 4-7, 10, 34-36, 40, and 42 under 35 USC 103(a) as being unpatentable over Boxer et al. in view of Keinanen et al., and of claim 3 as being unpatentable

over the noted references and further in view of Gutsman et al., are withdrawn in response to Applicant's arguments (see pages 13-17).

6. The rejections of claims 1-2, 4-7, 10, 34-36, 40, and 42 on the grounds of obviousness-type double patenting are withdrawn in response to Applicant's arguments (see pages 17-19).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-7, 10, 34-36, and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims lack a written description for the following reasons. Independent claim 1 is drawn to a method for assaying an interaction between a test agent and a lipid bilayer-associated component, where binding is detected by detecting a decrease in membrane fluidity.

The claims encompass detection of binding by change in membrane fluidity between a genus of test agents to a genus of lipid bilayer-associated components. The genus of test agents is large and of substantial variance, and includes small molecules, cell surfaces, vesicles, lipid-covered glass beads, and other agents (see claims 34-36 and 42). The claimed genus of lipid bilayer-associated components that interact with test agents is also characterized by substantial

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variance, and includes proteins, nucleic acids, glycolipids, lipopolysaccharide, sterols, lipid-linked molecules, fatty acids, and endotoxins (claims 2-3). However, the claimed genera of test agents and lipid bilayer-associated components have no disclosed partial structure, shared physical and/or chemical properties, or shared functional or other relevant identifying characteristics. In particular, there is no disclosure of that the genera of test agents/lipid bilayer-associated components are known to affect physical properties of the bilayer upon interaction. *There is no disclosure of any relevant identifying characteristics shared by test agents/ lipid bilayer-associated components that have the capacity to decrease membrane fluidity upon binding.*

With regard to claims 34-36, there is no disclosure that small molecules, proteins other than cholera toxin subunit B (CTB), cells, vesicles, phantom cells, liposomes, giant vesicles, lipid-covered glass beads, or “any component of any thereof” are known to affect the membrane fluidity of the bilayer upon interaction.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include “level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.” MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. The MPEP states that:

“The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice ...or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus” MPEP 2163.

In the instant case, the specification discloses only a single test agent (CTB) that is capable, upon interaction with a lipid bilayer-associated component (ganglioside GM1), of changing the membrane fluidity of the bilayer (see p. 23, lines 9-12 in particular). There are no working examples of other test agent-component pairs.

Scope of Enablement

9. Claims 1-7, 10, 34-36, and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for while being enabling for assaying an interaction between test agents that are bacterial endotoxins such as CTB and lipid bilayer-associated components that are endotoxin receptors such as ganglioside GM1, or for assaying interactions using test agents that are antibodies, does not reasonably provide enablement for assaying an interaction with all test agent-component pairs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The nature of the invention relates to a method for assaying an interaction between a test agent and a lipid bilayer-associated component that is part of a substrate-supported bilayer. The method for assaying an interaction includes the step of contacting the device with the test agent, so as to allow the test agent to bind to its lipid bilayer-associated ligand. Binding is detected

indirectly by evaluating membrane fluidity, where a decrease in membrane fluidity indicates that binding of the test agent to the lipid bilayer-associated component has occurred (see especially the specification at p. 14, lines 13-15 and p. 26, lines 3-14, which states that “[i]n accordance with the present invention, binding events are detected through their effects on one or more physical properties of the lipid bilayer, such as membrane fluidity”).

The claims are broadly drawn to methods of assaying binding between a large number of possible test agents and lipid bilayer-associated components, where the interaction is detected by evaluating the membrane fluidity. The genus of test agents is one of substantial variance, including such diverse species as small molecules (claim 34), proteins (claims 35 and 42), “a surface of a cell, a vesicle, a phantom cell, a plasma membrane vesicle, a liposome, a giant vesicle, a lipid-covered glass bead, or a component of any thereof” (claim 36). See also the specification at p. 3, lines 6-12, which discloses that test agents may include small molecules, polypeptides, antibodies, biomolecules, cell surfaces, vesicles, and phantom cells, for example.

The specification discloses CTB as an example of a test agent, which, upon binding to the lipid bilayer-associated ganglioside GM1, can affect the fluidity of lipid molecules in the neighborhood of the ganglioside (p. 14, line 33 to p. 15, line 4). The specification also provides working examples demonstrating that binding of CTB to membranes presenting GM1 may be detected indirectly by evaluating changes in membrane fluidity (Examples 3-4). The examples evaluate membrane fluidity by FRAP (Example 3) and by electrophoresis (Example 4).

The prior art teaches that the important feature in the interaction of CTB with ganglioside GM1 is *polyvalent binding*, as up to five GM1 receptors can bind to each cholera toxin molecule (Song et al., US Patent No. 6,297,059, column 8, lines 32-40 and column 6, lines 6-9). The

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interaction of cholera toxin with GM1 is therefore able to bring two or more GM1 receptors into close proximity (column 6, lines 1-5), which can be measured by fluorescence self-quenching or FRET (column 5, lines 49-51 and column 7, lines 44-67 in particular).

Therefore, unlike the large polyvalent CTB, binding of other test agents such as small molecules to bilayer-associated ligands would not necessarily have effects on membrane fluidity and other physical properties of the bilayer in light of the prior art teaching of the importance of polyvalent binding.

In fact, the prior art teaches that not all molecules are known to be capable of decreasing membrane fluidity upon binding to lipid bilayers. Moran et al. "Effect of Tocopherol and Taurine on Membrane Fluidity of Retinal Rod Outer Segments," (1987) *Exp. Eye Res.* **45**:769-776, the abstract and p. 775, lines 10-12) teach that the small molecule taurine has no effect on membrane fluidity upon interaction with membranes.

See also Altstiel et al. ("Structural Changes in BHK Cell Plasma Membrane Caused by the Binding of Vesicular Stomatitis Virus" *Journal of Virology* (1981) Vol. 39, p. 82-86), which teaches that "[l]igands that are monovalent or have reduced valency are generally unable to induce clustering of receptors in the plane of the plasma membrane" (p. 82, right column).

See also Paul et al. (US 5,770,570), which teaches that "[b]inding of polypeptides by membranes can lead to qualitatively similar *or opposing effects* on fluidity at different depths in the bilayer" (column 14, lines 23-31, emphasis added).

Binding of some test agents can also have the opposite effect of *increasing* membrane fluidity, as taught by Aguedo et al. ("Interaction of an odorant lactone with model phospholipids bilayers and its strong fluidizing action in yeast membrane" *International Journal of Food*

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Microbiology 80 (2003) 211-215), which teaches that interaction of γ -decalactone with a membrane-associated component (acyl chains of phospholipids) increases rather than decreases membrane fluidity (see especially the abstract and p. 214).

Thus, the prior art recognizes that not all test agents would be expected to cause changes membrane fluidity upon binding to a lipid bilayer-associated component, in that binding of test agents may increase, decrease, or alternatively have no effect upon membrane fluidity.

The specification provides no examples of test agents other than CTB that affect membrane fluidity or other physical properties upon binding. There are no working examples of other test agent/bilayer-associated component pairs that demonstrate such effects upon interaction.

The claims also encompass test agents interacting with lipid bilayer-associated integral membrane proteins. The prior art teaches that integral membrane proteins in supported bilayers may often be non-functional, and therefore incapable of interacting with test agents. Boxer et al. teach that:

[I]ntegral membrane proteins are immobile or exhibit severely restriction motion in supported bilayers. It is presumed that this is a result of interactions between the membrane protein and the solid support; there have been relatively few careful studies of the functional consequences of this interaction, but it is generally thought that these interactions will reduce or eliminate protein function.

See Boxer et al., "Molecular transport and organization in supported lipid membranes" (2000) *Curr. Opin. Chem. Biol.* 4:704-9, p. 705, right column, "Softer surfaces and Tethering," lines 1-9). Boxer et al. further teach that "lipid bilayers and membrane proteins are notoriously difficult to work with" (*ibid*, p. 704, right column, lines 14-15). The instant specification discloses that "[o]bservations of labeled CTB indicate that it is relatively immobile when bound

to supported membranes” (p. 34, lines 21-22). From the above teachings of Boxer et al., this may indicate that CTB is non-functional, and would therefore be incapable of interacting with test agents. This would be of particular relevance to claim 3, in which bacterial endotoxins may be the lipid bilayer-associated component that interacts with test agents. The examiner notes that claim 3 is in contrast with the examples presented in the disclosure, in which CTB is the *test agent*, rather than the *lipid bilayer-associated component*. The specification does not disclose any working examples where CTB is the lipid bilayer-associated component. Further, if immobilized CTB is immobile, it is unclear how it would be able to aggregate (cluster) upon binding by a test agent, and therefore decrease membrane fluidity.

More generally, the specification does not provide direction regarding the preservation of function of integral membrane proteins or other lipid bilayer-associated components. There are no working examples of functional lipid bilayer-associated components that interact with test agents, other than ganglioside GM1.

In summary, the prior art as well as the post-filing literature cited in the Declaration filed 2/2/06 establishes that the test agent-component pair of CTB-ganglioside GM1 has particular characteristics (such as polyvalency and large size) that allow for indirect detection of interaction by changes in the membrane fluidity. However, these characteristics are not shared by all test agent-component pairs encompassed by the claims. The prior art also teaches the unpredictability of preparing functional lipid bilayer-associated components such as integral membrane proteins, as well as the unpredictability in observing changes in membrane fluidity upon binding by all test agents, especially those that are monovalent. Therefore, due to the state of the prior art, which teaches that not all test agents have effects on membrane fluidity, the lack of

direction/guidance presented in the specification regarding detection of interactions by evaluation of physical properties where the test agent-component pairs are other than CTB/GM1, the lack of working examples directed to same, and the breadth of the claims, the specification fails to teach the skilled artisan how to make and use the claimed invention without undue experimentation.

Response to Arguments

10. Applicant's arguments filed 4/24/07 have been fully considered.

11. With respect to the rejection of claims 1-7, 10, 34-36 and 40 under 35 USC 112, 1st paragraph as failing to comply with the written description requirement, Applicant's arguments (see pages 8-11) have been fully considered but are not persuasive.

Applicant argues that Applicants should not need to show test agents and lipid bilayer-associated components to which they know will bind, since the purpose of the assay is to determine binding (see page 9). This is not found persuasive for reasons of record, since at issue is whether all binding events would result in detectable changes in membrane fluidity. In particular, the specification presents a single example in which binding of a test agent (cholera toxin) to a lipid bilayer-associated component (ganglioside GM1) was observed to decrease membrane fluidity. The specification makes particular mention of "[t]he large size and multivalent binding of [cholera toxin]" (page 34), which suggests that these properties may be influential in producing the detected changes in membrane fluidity upon binding. However, the claims are not limited to test agents that are of large size or which bind in a multivalent fashion.

It is maintained that skilled in the art would not envisage possession of methods involving any type of test agent and any type of lipid bilayer-associated component based on the single example of cholera toxin binding to GM1, given that the specification makes particular mention of the large size and multivalent binding capacity of cholera toxin, and in the absence of evidence to show that all test agents, upon binding to a lipid bilayer-associated component, would possess the claimed functional characteristic of being able to produce detectable changes in membrane fluidity.

Given such facts, and because Applicant is arguing that the claimed invention is distinguished over the prior art in that detection of binding events occurs indirectly by detecting changes in membrane fluidity (see for example pages 15-16 of the Reply), the burden is on Applicant to establish that binding events generally and universally produce detectable changes on membrane fluidity (see also the Interview Summary mailed 3/20/07).

In this regard, Applicant refers to seven articles purported to demonstrate the effects of diverse small molecules and peptides on membrane fluidity (see pages 9-10 of the Reply). However, because Applicant's amendment does not include copies of the references, any teachings therein cannot be evaluated.

Applicant also refers to Example 12 of the Written Description Guidelines, and argues that providing a surface array detector device was known in the art as evidenced by US 6,228,326 and methods for evaluating membrane fluidity are known in the art (see page 10). However, the claimed invention relates to a method of using a surface detector array device to detect binding by evaluating membrane fluidity; whether methods for evaluating membrane

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fluidity *per se* is immaterial since there is no evidence of record to indicate that such methods were known in the art for the purpose of detecting binding events.

With respect to claim 3, Applicant argues that cholera toxin (CTB) is an exotoxin rather than an endotoxin, and that the prototypical example of an endotoxin is LPS (see Reply, page 11). The examiner appreciates Applicant's clarification in this regard; however, the rejection is maintained for reasons of record in that although LPS is exemplified as the lipid bilayer-associated component in the single working example of the application, the claims are not limited with respect to the type of test agent.

With respect to the rejection of claims 1-7, 10, 34-36 and 40 under 35 USC 112, 1st paragraph (scope of enablement), Applicant's arguments (see pages 11-13) have been fully considered but are not persuasive.

Applicant argues that Example 7 of the specification, which involves cholera toxin and GM1 binding, is merely exemplary (pages 11-12), which is not persuasive since as discussed above, the specification makes particular mention of the large size of cholera toxin and the multivalent nature of this binding event, while as noted above the claims are not limited with respect to the size of the test agent or to detection of multivalent binding. Applicant also refers to the literature cited, but as noted above, since copies of the articles were not submitted to the Office for consideration, they have not been considered.

Applicant also argues that methods were known in the art to enhance the activity of integral membrane proteins in supported bilayers (see page 12); however, such arguments are not persuasive since the methods Applicant refers to (e.g., polyethylene glycol cushions) are not recited in the claims. In addition, Applicant is referring to the *non-patent literature publication*

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by Wagner and Tamm; Applicant is reminded that essential material (i.e., material that is necessary to provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112) may be incorporated by reference, but **only** by way of an incorporation by reference to a U.S. patent or U.S. patent application publication. MPEP 608.01(p).

Applicant further argues that methods for evaluating membrane fluidity were known in the art as evidenced by the '326 patent (see pages 12-13). This is not on point because at issue is not whether methods for evaluating membrane fluidity *per se* were known, but rather whether methods for detecting binding by detecting changes membrane fluidity were known. Such methods are not, to the Examiner's knowledge, disclosed in the '326 patent.

It is noted that Applicant has amended the independent claim to indicate that binding is detected by a *change* in membrane fluidity, such that decreases in fluidity (as previously claimed) or alternatively increases in fluidity may indicate binding. Although the amendments address some of the issues raised regarding the predictability of the art, the rejection is maintained for reasons of record as set forth above. In particular, given that the prior art teaches that some binding events have no effect on membrane fluidity (see the example of taurine discussed in the rejection above), it is maintained that the specification fails to predictably enable one skilled in the art to carry out the claimed method with any type of test agent-lipid bilayer-associated component pair.

12. Applicant's arguments (see Reply, pages 13-17) with respect to the rejections of claims 1-2, 4-7, 10, 34-36, 40, and 42 under 35 USC 103(a) as being unpatentable over Boxer et al. in view of Keinanen et al., and of claim 3 as being unpatentable over the noted references and further in view of Gutsman et al. have been fully considered and are persuasive. The rejection has been withdrawn. In particular, Applicant's arguments that Keinanen et al., in measuring "aggregation", are not in fact measuring membrane fluidity (see especially pages 15-16 of the Reply), are found persuasive.

13. Similarly, the rejections of claims 1-2, 4-7, 10, 34-36, 40, and 42 on the grounds of obviousness-type double patenting over Boxer et al. in view of Keinanen et al. are similarly withdrawn in response to Applicant's arguments (see pages 17-19).

Allowable Subject Matter

14. Claim 42 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

15. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

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the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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